UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,603	11/24/2003	Ananda M. Chakrabarty	51282-00013	6398

7590 08/08/2007

Sheppard Mullin Richter & Hampton LLP
1300 I Street NW
11th Floor East
Washington, DC 20005-3314

EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
08/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/720,603	CHAKRABARTY ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *11-19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Argument and Amendment

The Amendment filed on 7/6/2007 in response to the previous Non-Final Office Action (4/6/2007) is acknowledged and has been entered.

Claims 1-10 have been amended. Claims 1-21 are pending Claims 11-19 and 21 have been withdrawn for non-elected invention previously. Claims 1-10 and 20 are under consideration.

It is noted that the set of amended claims filed on 7/12/2007 is identical to the claims filed on 7/6/2007 and lists as a different U.S. serial No on the claims. After telephone conversation with Mr. Pelto on 7/23/2007, who indicates the U. S. serial No as 11/244105 on the claim paper filed on 7/12/2007 is typographic error and correct U. S. serial No should be 10720603.

The following office action contains NEW GROUNDS of rejection.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 7/13/2007 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Sequence Requirements

It is acknowledged that the specification is amended by adding SEQ ID Nos on [026] figure 11.

Rejections Withdrawn

1. The rejection of c Claims 1-10 and 20 under 35 U.S.C. 112, second paragraph, as being unclear what the effective amount in the method is withdrawn in view of the amendments to the claims by deleting the term.

2. The rejection of claims 1-10 and 20 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the claimed method using variants or derivatives of cupredoxin is withdrawn in view of the amendments to the claims. However, the newly amended claims are subjected to the new rejection under 35 U.S.C. 112, first paragraph-enablement (see below).

3. The rejection of claims 1-2 and 20 under 35 U.S.C. 102(a) as being anticipated by Yamada et al., in view of the applicant's argument and amendment to the claims.

4. The rejection of claims 1, 3, and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18, 20, 21 of copending Application No. 11436592 is withdraw in view of the claims 18, 20, and 21 being withdrawn as non-elected invention in the currently prosecuted application 11436592, in which applicant elected peptide of cupredoxin (claims 1-17, 28, and 29) for examination.

Rejections Maintained

1. Claims 1, 3, and 20 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-22 of copending application 11488693 for the reasons of record in the prior Office Actions (11/24/06, page 9 and 4/24/2007, page 9-10). Applicant does not respond to this rejection in the remark filed on 7/6/2007.

2. Claims 1-6 and 20 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, and 7-12 of US patent No. 7084105 in view of Yamada et al., for the reasons of record in the prior Office Actions (4/24/2007, page 11-12). Applicant states that the addressing the present rejection is deferred until there is allowable subject matter in the present application and at that time a terminal disclaimer will be filed if warranted by the examiner's rejection in view of the allowed claims. The rejection will be maintained until its is obviated.

Rejection Maintained and Response to Arguments

Priority

The effective filing date of 8/15/2003 established previously for claims 1, 2, 9 and 10 as stated in the previous office actions is maintained. The effective filing date of 8/15/2003 is currently established for amended claims 5 and 6 reciting mutant or truncated azurin.

Applicant argues that supports for the subject claims are found in provisional application 60/269133, figure 1-15, and non-provisional application 10/047710, figure 1-8 and examples 1-16 etc. In response to this argument, as stated in the previous office action, administering plastocyanin as a species of cupredoxin for in vivo treating a patient or binding to p53 of claimed method are NOT described any

place including figures, examples, and texts in those priority documents, which only described wild type azurin being administering to a subject. Therefore, again the effective filing date for the claims above is given as 8/15/2003.

Rejection under 35 USC § 112, first paragraph-written description

Claims 1-10 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement stated again as below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The claims are amended as drawn to a method of treating a condition related to resistance to cell death comprising administering cupredoxin, wherein the cupredoxin is an azurin comprising mutated or truncated azurin (claim 5). The response filed on 7/6/2007 states that *specification, paragraph 112-120, discloses the mutation and/or truncation of cupredoxins which have cytotoxic activity and how to develop a truncated or mutant cupredoxin from azurin or plastocyanin* (page 8, para 3). In response to this argument, first, the paragraphs 112-120 of specification teach a method of making mutants and fragments of azurin, not other cupredoxin comprising elected species plastocyanin. While claimed method is drawn to *in vivo* treating a patient by administering any cupredoxin comprising the mutant and truncated azurin and other species of cupredoxin. However, the specification only provides the teaching on treating a subject with wild type of azurin, not other cupredoxin including elected species of plastocyanin and mutants or truncated azurin of SEQ ID NO: 6 and 7. As such, one skilled in the art would not convince that the applicant had the possession of the claimed method of using any form of cupredoxin except of wild type of azurin.

Applicant then argues the chemical structures of functional attribute of the genus of the variants, derivatives, mutants have been described in the specification (page 9) and also argue that the specification teaches how to develop mutants of azurin is used for in vitro assay and treating a tumor

(page 10 line 3-5). In response to the argument, the term variants and derivatives of cupredoxin in the claims have been deleted. The prophetic variants derivatives that applicant discussed on page 9 and 10 do not provide adequate support of the specific truncated form of azurin that would maintain the required function. One skilled in the art has recognize some truncated azurin does not have the same function as wild type azurin. For example, Yamada et al., (PNAS, vol 99, page 14098-14103, provided in previous office action) show "mutations in two critical amino acids Met-44 and Met-64 of azurin have been shown to lead to a loss of >95% of the azurin electron transfer activity. Current claims are amended to include mutants and truncated of azurin that are disclosed in the specification, for example, as amino acid sequences of SEQ ID NO: 6 and 7 etc, however, the description of the structure of the mutants and how to make such mutants do not render applicant having a possession of using the mutants, especially using them to treat a disease condition without described method step by reduced practice of claimed method. Description of an in vitro assay of cytotoxicity to the cancer cells do not render applicant having a possession of in vivo treating a patient with cancer. Regarding to the correlation between in vitro assay and a method of in vivo treatment as well as providing example in the specification stated on page 9-10 will be discussed in detail below in the enablement rejection. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

The following is a New Ground of rejection-based on the amendment to the claims

Claim Rejections - 35 USC § 112-scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a condition related to resistance to cell death comprising administering to a patient a pharmaceutical composition of wild type azurin of SEQ ID NO: 1 does not reasonably provide enablement for the method of administering any other cupredoxin comprising elected

plastocyanin and mutated or truncated azurin comprising amino acid sequence of SEQ ID NO: 6 and 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of necessary experimentation claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The claims are broadly drawn to a method of treating a condition related to resistance to cell death comprising administering to a patient a pharmaceutical composition comprising any cupredoxin. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. Thus, it would be expected that one of skill in the art would be able to treat a condition with any cupredoxin comprising species of plastocyanin and mutated or truncated azurin without undue experimentation by using the claimed method.

The specification on page 44-47 (examples 15-16 and 18) describes in vivo treating mice with azurin with or without other agent. For the enablement disclosure of claimed invention, examples 16 teaches that mice with melanoma tumor were treated with wild type azurin plus M. *Bovis* column chromatographic fractions (QSFT) without the presence of azurin (figure 8). The specification does not provide a method of in vivo treating a condition to induce cell death in tumor cell with any other cupredoxin comprising species of plastocyanin and any mutated or truncated azurin. The specification although provides the structures of mutated or truncated azurin such as amino acid sequences of SEQ ID NO: 6 and 7, an *in vitro* assay indicates that the most of the mutated or truncated azurin do not work as well as the wild type of azurin in term of the cytotoxicity to the cells (figure 12-13). The method of claimed mutated azurin of SEQ ID NO: 7 shows minimal cytotoxic activity to the cells (figure 12). In addition, claimed invention is drawn to *in vivo* treating a condition with mutated or truncated azurin or any cupredoxin, however, the specification shows neither the result of in vivo treatment with the cupredoxin

(except wild type azurin), nor correlation between the in vitro cytotoxic activities and *in vivo* treatment in a patient. Thus, in the absence of this guideline, direction and experimentations, one skilled in the art would be unable to use claimed invention without an undue quantity of experimentations because the unpredictability of the nature of the invention.

One skilled in the art has recognized that the mutated or truncated form of a toxin may not always have the same activities as its wild type form. For example, Yamada et al., (PNAS, vol 99, page 14098-14103, provided in previous office action) show "mutations in two critical amino acids Met-44 and Met-64 of azurin have been shown to lead to a loss of >95% of the azurin electron transfer activity. The assay for cytotoxicity of the azurin against a human melanoma cell line UISO-Mel-2 demonstrate that the M44K/M64E mutant has very little cytotoxicity compared to the wild type of azurin (Fig. 2*B, page 14100 col 1*). Yamada et al., further teach that M44KM64E mutant being deficient in cytotoxicity toward a p53 null cell line UISO-Mel-6 cells is due to deficient in forming a complex with p53. Because claimed invention for *in vivo* treatment a condition is unpredictable and because one skilled in the art has recognized the mutated azurins do not have the activities as wild type azurin undo experimentation would be necessary and required in order to use and practice claimed invention by one skilled in the art.

Thus, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to the usage of any cupredoxin comprising elected species of plastocyanin and mutated or truncated azurin, one skilled in the art would be forced into under an undue quantity of experimentation in order to practice the broadly claimed invention. If applicants has any objective evidence contrary to the rejection, applicant is invited to submit it to the Office for reconsideration.

Response to applicant argument made to the last rejection under 35 USC 112-enablment, which in part may be applied to this rejection

The response filed on 7/6/2007 states (page 10):

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

And further states (page 11):

Applicants submit that the specification does indeed teach the induction of cell death, specifically via apoptosis, in the binding of cupredoxins to p53. Paragraph [081] teaches that "[a]zurin forms a complex with p53, stabilizes it... thereby inducing apoptosis. Further, whether mutant azurin proteins exhibit cytotoxic activity depends on whether there is continued ability of the mutant to form p53 complexes.

In response to this argument, the Office has provided strong evidence by Yamada et al., to show the mutated azurin (M44kM64E) does not have the cytotoxic activities as wild type of azurin above in the rejection. The office agrees the forming a complex between the wild type azurin and p53 is provided in the current application. However, the specification does not provide teaching such complex formed between the mutant azurin and p53 and Yamada et al., teach that lack of cytotoxic activities of mutant azurin is due to the deficiency of forming a complex between the p53 and the mutant azurin as discussed above in the rejection.

Applicant, on page 12, paragraph 1, also argues that *the specification provides teaching on how to make mutation and truncated azurin.* This has been discussed above in the rejection and again that teaching on how to make such variants of azurin does not enable a method of treating a condition with the variants because treating a disease with untested agent is unpredictable and requires undue experimentation.

Applicant, on page 12 paragraph 2, further argues that *the specification teaches in vivo treatment with azurin in example 15, 16 and 18 as well as teaches comparison studies between azurin and its mutants in vitro (example 20 and 21 and figure 12 and 13).* In response to this argument, as discussed in the rejection above, the examples only teach the in vivo treatment with wild type of azurin, not other species of cupredoxin or any variants/mutants of azurin. The specification does not provide a study of comparison or correlation between an *in vivo* model and *in vitro* cell assays. The examples and figures provide only *in vitro* cytotoxic activity of mutants and truncated azurin, which indicate that the most of azurin variants comprising claimed mutants of SEQ ID NO: 6 and 7 have less or no cytotoxic activities compared to wild type.

With regards to the correlation between in vitro assays and *in vivo* models, the state of the art recognizes that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic

physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are unpredictable and generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, vol12, page 320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, vol 278, page1041-1042, 1997) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated

with clonogenic assays. All of this underscores the criticality of providing workable examples, which is not disclosed in the specification, particularly in an unpredictable art such as cancer therapy.

Thus, Applicant's argument has not been found persuasive, and the rejection under USC 112, 1st paragraph as not being reasonably providing enablement for the method of treating a condition using any other cupredoxin comprising elected plastocyanin and mutated or truncated azurin of amino acid sequences of SEQ ID NO: 6 and 7 is maintained for the reason of the record and made again above.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Yamada et al., (PNAS, vol 99, page 14098-14103, provided in previous office action) teach that wild type of azurin exhibit cytotoxicity to melanom tumor or mice with the tumor. Yamada et al., do not teach or suggest treating resistant to cell death by administering truncated or mutated form of cupredoxin or plastocyanin.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY